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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/580,589	ROGUEDA, PHILIPPE	
	Examiner	Art Unit	
	JAMES H. ALSTRUM-ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2011*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-7 and 10-14* is/are pending in the application.

5a) Of the above claim(s) *10 and 13* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-7,11,12 and 14* is/are rejected.

8)☒ Claim(s) *5* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7 and 10-13 are pending. Claim 10 is withdrawn as being drawn to non-elected invention. Claim 13 is withdrawn as being drawn to non-elected species. Claim 14 is new. Applicant amended claim 5, but provided an incorrect claim status indicator for claim 5. **Claims 1-7 and 11-12 are under consideration in the instant office action**. Receipt and consideration of Applicant's remarks/arguments submitted on June 30, 2011 are acknowledged. All rejections/objections not explicitly maintained in the instant office action have been withdrawn per Applicant's claim amendments and/or persuasive arguments. Applicant's claim amendments have necessitated new grounds of rejection set forth below (*e.g.* under 35 U.S.C. §).

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 30, 2011 has been entered.

Election/Restrictions

The restriction requirement and species election, first mailed on October 1, 2009, **are maintained** at this time.

Claim Objections

Claim 5 is objected to because of the following informalities: there is an extraneous "square" on line 3 of claim 5, which does not appear to be a part of the named moiety of "beta-alanyl." Appropriate correction is required.

Claim Rejections - 35 USC § 112 (New Rejections Necessitated by Amendment)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter). The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. New claim 14 recites that the claimed formulation of claim 1 is "substantially free of a co-solvent" and Applicant indicates that support can be found on page 2, lines 1-10, especially, on page 2, lines 9-10 of the specification. The cited section of the specification only supports the notion of compositions **devoid** of co-solvent, whereas the phrase "substantially free of co-solvent" reads on formulations containing a finite, but small, amount of co-solvent.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is vague and indefinite, because it recites that the claimed formulation is "substantially free of co-solvent;" however, neither Applicant's claim nor specification define "substantially" or "substantially free." Consequently, the ordinary skilled artisan would be unable to ascertain the metes and bounds of claim 14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7, 11-12, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Muller et al. (WO 2003/066031) in view of Uekama et al. ("Cyclodextrin Drug Carrier

Systems," *Chem. Rev.* 1998, *98*, pp. 2045, 2048 (Table 2); and 2063), wherein US 2005/0085445 is being used as the English language equivalent of WO 2003/066031. All citations to Muller are to the English equivalent US publication.

Applicant Claims

Applicant claims a pharmaceutical composition comprising (i) any HFA (hydrofluoroalkane), (ii) a drug (dependent claim 6 limits the drug to those selected from a Markush group consisting of various drugs, including the elected drug, budesonide, and (iii) a partially or fully acylated alpha-, beta-, or gamma-cyclodextrin.

NOTE: The phrase "substantially-free of co-solvent" in new claim 14 is unclear, but has been interpreted to include amounts of co-solvent of ~10.0% w/w or less.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Muller teaches stabilized pharmaceutical **HFA suspension formulations** comprising (i) at least one pharmaceutical ingredient (e.g. **budesonide**), (ii) at least one propellant (e.g. HFA 227 or HFA 134a), (iii) **a native or modified alpha-, beta-, or gamma-cyclodextrine (e.g. hydroxypropyl-beta-cyclodextrine)**, and (iv) at least one hydrophilic additive (e.g. PEG or PVP) (title, abstract; [0014]-[0023]. Muller's preparation of the formulations involves **dissolving components (i) and (iii)-(iv) by mixing with ethanol** ([0029]). The solution formulation is transferred into a pressure-resistant container fitted with a metering valve and the suspension is formed upon addition to the solution formulation of the HFA propellant ([0029]-[0041]). Muller exemplifies the preparation of invented formulations wherein **the only drug is**

budesonide (Example 3: [0034]); the only drug is formoterol fumarate dihydrate (Example 4: [0035]); the only drug is salmeterol xinafoate (Example 8: [0039]); the only drug is fluticasone-17-propionate (Example 6: [0037]), and wherein the formulation comprises a combination of budesonide and formoterol fumarate dihydrate (Example 5: [0036]). Muller teaches that combinations **of active agents are also suitable** ([0022] and claim 3).

Muller's Example 1 composition comprises about 4.3% w/w ethanol (co-solvent), about 2.2% w/w PEG 200 (co-solvent), ~0.25% dissolved salbutamol, about 90% w/w HFA 227, and about 3.60% w/w of cyclodextrin, based on a total mass of 13.936 g. Thus, Muller's exemplified formulation of Example 1 is "substantially free of co-solvent," because it contains less than 10% w/w total co-solvent.

Uekama teaches that the most common pharmaceutical application of cyclodextrins is to enhance solubility, stability, and bioavailability of drug molecules, and that natural cyclodextrins generally exhibit poor water solubility (pp.
0. 2045). A variety of cyclodextrin derivatives are reported by Uekama and described in pharmaceutical applications, **including peracylated cyclodextrins, such as 2,3,6-tris-O-acetylcyclodextrin, 2,3,6-tri-O-hexanoylcyclodextrins, 2,3,6-tri-O-valerylcyclodextrins, etc.** (pg. 2047, Table 1; pg. 2048, Table 2, left column). The solubility behavior of various peracetylated-cyclodextr0ins in ethanol/water mixtures from 0% v/v ethanol to 100% v/v ethanol is depicted in Figure 2 on page 2048. **Compared to beta-cyclodextrin all but one of the peracylated cyclodextrins depicted in Figure 2 exhibited greater solubility in 100% ethanol**. Uekama also teaches **various peracylated cyclodextrins as being suitable to obtain prolonged-release pharmaceutical formulations** (pg. 2063, right column).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Muller lacks the teaching of formulations comprising partially or fully acylated cyclodextrins. This deficiency is cured by the teachings of Uekama.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify the teachings of Muller and utilize peracylated cyclodextrins in lieu of or in addition to hydroxy-propyl cyclodextrin, because it is well known in the art to modify the structure of naturally occurring cyclodextrins to obtain cyclodextrin derivatives exhibiting more desirable solubility properties and to stabilize active agents combined with the cyclodextrins. An ordinary skilled artisan would also have been motivated to utilize a peracylated cyclodextrin derivative, such as any one of those taught by Uekama, because these cyclodextrin derivatives can be used to prepare prolonged release drug formulations. It would be desirable to administer a prolonged release drug formulation in the instances, wherein the typical drug dosing regimens requires several daily administrations. A prolonged release dose would require the patient to remember fewer dosing events per day and would reasonably be expected to enhance patient compliance with pharmacotherapy. An ordinary skilled artisan would have had a reasonable expectation of obtaining HFA/drug/acylated drug formulations, because HFA/drug/hydroxypropyl cyclodextrin/drug formulations are known to be suitable and both hydroxypropyl cyclodextrin and the acylated cyclodextrins tested by Uekama are soluble in ethanol. Regarding claim 3 and the recitation of a solution, although Muller's end formulation is a suspension formulation, it is the Examiner's position that an ordinary skilled artisan would readily expect that solution formulations can be obtained by the addition of more solvent (i.e. ethanol). Therefore, the recitation of a solution formulation is considered to be prima facie obvious.

Regarding claim 7, Muller exemplifies a HFA formulation comprising both budesonide and formoterol fumarate dihydrate (Example 5: [0036]) and also teaches that combinations of

active agents are suitable ([0022] and claim 3). Thus, it would have been prima facie obvious to prepare HFA formulations comprising (i) budesonide, (ii) formoterol fumarate dihydrate, and (iii) acylated cyclodextrins. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 6/30/2011 have been fully considered but they are not persuasive. Applicant traverses the instant rejection arguing that (i) the cited references only teach the isolated components and allegedly fail to provide any motivation to modify Muller to utilize hydrophobic partially or fully acylated cyclodextrins, because Muller has a preference for hydrophilic cyclodextrins and the cited teachings of Uekema refer only to hydrophobic cyclodextrins; (ii) there is no reasonable expectation of success, because Muller does not teach the pulmonary administration of hydrophobic cyclodextrins and Uekema does not suggest that hydrophobic cyclodextrins are suitable for pulmonary administration; (iii) allegedly there is no disclosure of acylated cyclodextrins in Muller and Uekema that would motivate the ordinary skilled artisan to administer compositions comprising hydrophobic cyclodextrins pulmonarily or nasally; and (iv) new claim 14 excludes the presence of co-solvent.

The Examiner respectfully disagrees with and/or finds Applicant's traversal arguments unpersuasive. Regarding (i) and (iii), the motivation to modify the teachings of Muller to utilize acylated cyclodextrins stems from the prior teachings that acylated cyclodextrins are known to enhance drug solubility in ethanol, impart drug controlled release, and are suitable for

administration via a variety of conventional pharmaceutical routes. The fact that Uekema does not explicitly identify inhalation administration as one of the routes of administration for acylated cyclodextrins is not a fatal flaw, because the prior art recognizes that cyclodextrins can be administered by inhalation. Furthermore, there is nothing in the prior art or of record that would discourage the ordinary skilled artisan from including acylated cyclodextrins in an inhalable formulation or would lead the ordinary skilled artisan to conclude that acylated cyclodextrins are not compatible with inhalation administration.

Regarding (ii), Applicants are dismissive of the fact that both the hydrophilic cyclodextrins taught by Muller and the hydrophobic cyclodextrins taught by Uekema are soluble in ethanol. Applicants are mistaken to dismiss this teaching, because Muller explicitly utilizes ethanol to formulation aerosol formulations that can be administered pulmonarily. Thus, the ordinary skilled artisan is provided with a reasonable expectation of successfully formulating Uekema's hydrophobic cyclodextrins into Muller's formulations, which are intended for pulmonary administration. Furthermore, given that Uekema's hydrophobic cyclodextrins are known to enhance drug solubility in ethanol, there is added motivation for the ordinary skilled artisan to include Uekema's hydrophobic cyclodextrins in aerosol formulations intended for pulmonary administration, such as are taught by Muller.

Additionally it is noted that the teachings of the combined prior art are not required to have the same motivation as Applicant. Thus, the stated motivation for combining the teachings of the cited prior art reference are proper and contrary to Applicant's assertion the rejection is based upon motivation provided by the prior art references. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Regarding (iv), Applicant's claims use open "comprising" claim language and do not exclude co-solvent. Additionally, it is the Examiner's position that a broad and reasonable interpretation of the phrase "substantially free of co-solvent" is an amount of co-solvent that is 10% w/w or less, absent evidence to the contrary and in light of the fact that Applicant does not define this phrase in claim 14 or in the specification. Consequently, the combined prior art provides examples of formulations containing less than 10% w/w co-solvent, which is considered to provide adequate guidance to the ordinary skilled artisan to obtain HFA/cyclodextrin pharmaceutical formulations that are "substantially free of co-solvent." The rejection is maintained.

Conclusion

Claims 1-7, 11-12, and 14 are rejected. Claims 10 and 13 are withdrawn from consideration. No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, ~10:00-6:00 and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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